

Pharmacokinetics

Metabolism

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions

Phase I reactions:

- Oxidation, reduction, hydrolysis.
- Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase.
- Products of phase I reactions are typically more active and potentially toxic

Phase II reactions:

- Conjugation.
- Products are typically inactive and excreted in urine or bile.
- Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved

The majority of phase I and phase II reactions take place in the liver

First-pass metabolism

- This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism.
- As a consequence much larger doses are needed orally than if given by other routes.
- **This effect is seen in many drugs, including:**
 - 1) aspirin
 - 2) isosorbide dinitrate
 - 3) glyceryl trinitrate GTN
 - 4) lignocaine
 - 5) propranolol
 - 6) verapamil
 - 7) isoprenaline
 - 8) testosterone
 - 9) hydrocortisone

Questions concerning zero-order kinetics and acetylator status are also common in the exam

Zero-order kinetics

- Zero-order kinetics describes metabolism which is independent of the concentration of the reactant.
- This is due to metabolic pathways becoming saturated resulting in a constant amount of drug being eliminated per unit time.
- This explains why people may fail a breathalyser test in the morning if they have been drinking the night before

Drugs exhibiting zero-order kinetics:

- 1) phenytoin
- 2) salicylates (e.g. high-dose aspirin)
- 3) heparin
- 4) ethanol

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Acetylator status

50% of the UK populations are deficient in hepatic N-acetyltransferase

Drugs affected by acetylator status

- 1) isoniazid
- 2) procainamide
- 3) hydralazine
- 4) dapsone
- 5) sulfasalazine

P450 enzyme system

- Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inducers of the P450 system

- 1) smoking (affects CYP1A2, reason why smokers require more aminophylline)
- 2) chronic alcohol intake
- 3) phenytoin, carbamazepine (antiepileptics)
- 4) phenobarbitone (barbiturates)
- 5) rifampicin
- 6) St John's Wort
- 7) griseofulvin

Inhibitors of the P450 system

- 1) ciprofloxacin, erythromycin, quinupristin (antibiotics)
- 2) isoniazid
- 3) imidazoles: ketoconazole, fluconazole
- 4) ritonavir
- 5) cimetidine, omeprazole
- 6) amiodarone
- 7) allopurinol
- 8) SSRIs: fluoxetine, sertraline
- 9) sodium valproate
- 10) acute alcohol intake

P450 drug interactions: more detail

Whilst you are expected to know in broad terms what are the main inhibitors and inducers of the P450 system it is unlikely that you will be asked detailed questions about the individual enzyme systems.

It is worthwhile noting that the most important and common reason for drug interactions is the P450 CYP3A4 system.

The table below shows the main enzyme systems that are affected by common drugs. There is clearly a lot of overlap within the various P450 enzymes.

P450 system	Substrates	Inhibitors	Inducers
CYP3A4	Macrolides Antiretrovirals Calcium channel blockers	Macrolides Protease inhibitors (including ritonavir) Imidazoles	Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort
CYP2D6	Tricyclic antidepressants Antipsychotics	SSRIs Ritonavir	
CYP2C9	Warfarin Sulfonylureas	Imidazoles Amiodarone Sodium valproate	Rifampicin
CYP1A2	Theophylline	Ciprofloxacin	Smoking Omeprazole
CYP2E1	Alcohol		Chronic alcohol Isoniazid

Drugs which act on serotonin receptors

- It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis

Agonists:

- 1) **sumatriptan** is a **5-HT_{1D} receptor agonist** which is used in the acute treatment of migraine
- 2) **ergotamine** is a **partial agonist of 5-HT₁ receptors**

Antagonists:

- 1) **Pizotifen** is a **5-HT₂ receptor antagonist** used in the prophylaxis of migraine attacks.
- 2) **Methysergide** is another **antagonist of the 5-HT₂ receptor** but is rarely used due to the risk of **retroperitoneal fibrosis**
- 3) **Cyproheptadine** is a **5-HT₂ receptor antagonist** which is used to control diarrhoea in patients with carcinoid syndrome

5-HT₃ antagonists

- 5-HT₃ antagonists are **antiemetics** used mainly in the management of **chemotherapy related nausea**.
- They mainly act in the chemoreceptor trigger zone CTZ area of the medulla oblongata.

Examples:

- **ondansetron**
- **granisetron**

Adverse effects:

- constipation is common

Drugs used in Hyperlipidaemia:

Mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs	Mechanism of action	Adverse effects
Statins	HMG CoA reductase inhibitors	Myositis, deranged LFTs
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	Agonist of PPAR-alpha therefore increases lipoprotein lipase expression	Myositis, pruritus, cholestasis
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

Current guidelines for lipid lowering*

	Total cholesterol (mmol/l)	LDL cholesterol
Joint British Societies	< 4.0	< 2.0
National Service Framework for CHD	< 5.0	< 3.0
SIGN 2007	< 5.0	< 3.0

NICE guidelines on Cardiovascular disease (CG181) recommend aiming for cholesterol <4 mmol/L and LDL-C <2 mmol/L in diabetic patients.

Beta-blocker overdose

Features:

- bradycardia
- hypotension
- heart failure
- syncope

Management:

- if bradycardic then **atropine**
 - in resistant cases **glucagon** may be used
 - **Haemodialysis** is not effective in beta-blocker overdose
- Overdose of beta-blockers or calcium channel blocker can lead to significant bradycardia.
 - If taken **within one hour** of presentation, **activated charcoal** should be tried.
 - If there is symptomatic bradycardia **atropine** should be used **in the first instance**.
 - **Glucagon** can be effective but this should be tried after atropine.
 - Pacing may be necessary if these drug treatments fail.

Calcium channel blockers

- Calcium channel blockers are primarily used in the management of cardiovascular disease.
- Voltage-gated calcium channels are present in:
 - 1) myocardial cells,
 - 2) cells of the conduction system
 - 3) the vascular smooth muscle cells

The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

Examples	Indications & notes	Side-effects and cautions
Verapamil	☒ Angina, hypertension, arrhythmias • Highly negatively inotropic • Should not be given with beta-blockers as may cause heart block • Should not be given in ventricular tachycardia	1) Heart failure, 2) hypotension, bradycardia, 3) flushing 4) constipation
Diltiazem	☒ Angina, hypertension • Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers	1) heart failure 2) Hypotension, bradycardia, 3) ankle swelling
Nifedipine, amlodipine, felodipine (dihydropyridines)	☒ Hypertension, angina, Raynaud's • Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure	1) Flushing, headache, 2) ankle swelling

Adrenaline

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties

Indications:

- anaphylaxis
- cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses:

- 1) anaphylaxis: 0.5ml 1:1,000 **IM**
- 2) cardiac arrest:
 - ⇒ 1ml of 1:1000 **IV**
 - ⇒ 10ml 1:10,000 **IV**

Management of accidental injection:

- local infiltration of phentolamine

Adrenoceptor antagonists

Alpha antagonists

- alpha-1: doxazosin
- alpha-1a: tamsulosin - acts mainly on **urogenital tract**
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Mixed alpha and beta antagonists

- Carvedilol and labetalol

Finasteride

Finasteride is an **inhibitor of 5 alpha-reductase**, an enzyme which metabolises testosterone into dihydrotestosterone

Indications:

- 1) benign prostatic hyperplasia
- 2) male-pattern baldness

Adverse effects:

- 1) impotence
- 2) decrease libido
- 3) ejaculation disorders
- 4) gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum PSA

Allopurinol

- Allopurinol is used in the prevention of gout.
- It works by inhibiting xanthine oxidase

Initiating allopurinol prophylaxis - see indications below

- 1) allopurinol should not be started until 2 weeks after an acute attack has settled
- 2) initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of $< 300 \mu\text{mol/l}$
- 3) NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol*

- 1) recurrent attacks
 - ⇒ the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- 2) tophi
- 3) renal disease
- 4) uric acid renal stones
- 5) prophylaxis if on cytotoxics or diuretics

*patients with **Lesch-Nyhan syndrome** often take **allopurinol for life**

Interactions

1) Azathioprine:

- Azathioprine metabolised to active compound 6-mercaptopurine
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- allopurinol can therefore lead to high levels of 6-mercaptopurine
- a much reduced dose of AZA (e.g. 25%) must therefore be used if the combination cannot be avoided

2) Cyclophosphamide

- allopurinol reduces renal clearance, therefore may cause marrow toxicity

Allopurinol Hypersensitivity Syndrome (AHS)

- 0.1-0.4 % allopurinol treated patients develop allopurinol hypersensitivity syndrome (AHS)
- This can present as a severe multi-organ disease, with rash, hepatic and renal dysfunction, eosinophilia, and vasculitis, and has 20-25% mortality.
- Risk factors for this include renal impairment, thiazide diuretic use, and recent initiation of allopurinol (weeks/months).
- AHS is caused by the direct toxic effects of oxypurinol, or by T cell activating effects of oxypurinol, allopurinol. Patients with AHS should not be rechallenged with the drug.
- 2% of patients on allopurinol develop itchy maculopapular rashes
- 5-10% develop gastrointestinal dysfunction, and deranged liver function tests (LFTs)
- Allopurinol increases the anticoagulant effect of warfarin
- 20% of patients on allopurinol, who are prescribed amoxicillin or ampicillin, develop a rash.

Antihistamines

- Antihistamines (H₁ inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

Examples of sedating antihistamines:

- chlorpheniramine
- As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth).

Examples of non-sedating antihistamines

- loratidine
- cetirizine

Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.

Motion sickness

- Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement

Management:

- 1) BNF recommends **Hyoscine** (e.g. transdermal patch) as being the most effective treatment. Use is limited due to side-effects
- 2) Non-sedating antihistamines such as **cyclizine** or **cinnarizine** are recommended in preference to sedating preparation such as promethazine

Monoamine oxidase inhibitors MAOI

- serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell
- Non-selective monoamine oxidase inhibitors
 - e.g. **tranylcypromine**, **phenelzine**
 - used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
 - not used frequently due to side-effects

Adverse effects of non-selective monoamine oxidase inhibitors:

- 1) **hypertensive reactions** with tyramine containing foods
e.g. cheese, pickled herring, الرنجة Bovril, Oxo, Marmite, broad beans
- 2) **anticholinergic effects**

Tricyclic Antidepressants

- TCAs are used less commonly now for depression due to side-effects & toxicity in overdose.
- They are however used widely in the treatment of **neuropathic pain**, where smaller doses are typically required.

Common side-effects:

Due to antimuscarinic side effects more common with **imipramine**

- 1) **Drowsiness**, **tachycardia**
- 2) dry mouth
- 3) blurred vision, **Mydriasis** (dilated pupils)
- 4) constipation
- 5) urinary retention

Choice of tricyclic:

- 1) **low-dose amitriptyline** is commonly used in:
 - ✓ the management of **neuropathic pain** and
 - ✓ the prophylaxis of **headache** (both tension and migraine)
- 2) **lofepramine** has a lower incidence of toxicity in overdose
- 3) **amitriptyline** and **dosulepin** (dothiepin) are considered **the most dangerous in overdose**

More sedative	Less sedative
Amitriptyline	Imipramine
Dosulepin	Lofepramine
Clomipramine	Nortriptyline
Trazodone*	

*trazodone is technically a 'tricyclic-related antidepressant'

Tricyclic overdose

- Overdose of TCAs is a common presentation to emergency departments
- Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.

Early features relate to **anticholinergic** properties:

- 1) **Agitation**, dry mouth,
- 2) **dilated pupils**, blurred vision
- 3) **sinus tachycardia**,
- 4) constipation, urinary retention

Features of severe poisoning include:

- 1) arrhythmias
- 2) seizures
- 3) metabolic acidosis
- 4) coma

ECG changes include:

- 1) sinus tachycardia
- 2) prolongation of QT interval
- 3) widening of QRS
 - ⇒ Widening of QRS > **100ms** is associated with an increased risk of **seizures**,
 - ⇒ whilst QRS > **160ms** is associated with ventricular **arrhythmias**

Management:

- 1) **IV bicarbonate** may reduce the risk of seizures and arrhythmias in severe toxicity
- 2) arrhythmias:
 - ⇒ Response to **lignocaine (1b)** is **variable** and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
 - ⇒ ~~Class 1a (e.g. Quinidine)~~ and ~~class Ic~~ antiarrhythmics (e.g. Flecainide) are **contraindicated** as they **prolong depolarisation**.
 - ⇒ ~~Class III drugs such as amiodarone~~ should also be **avoided** as they **prolong the QT interval**.
- 3) intravenous lipid emulsion (**intralipid**) is increasingly used to bind free drug and reduce toxicity
- 4) dialysis is **ineffective** in removing tricyclics (however can be used for acidosis refractory to NaHCO₃)

- TCAs can cause SIADH
- If **BZD + TCA toxicity** do not give **flumazenil** as it reduces its **seizure threshold**

A 19-year-old man was admitted to the Emergency department from the inpatient psychiatric unit. He had a known history of severe depression and his admission to the psychiatric unit had been arranged from the community. However, shortly after arriving in the psychiatric unit he collapsed. An empty pill bottle was found in his pocket.

On admission to the emergency unit he was semi-conscious. His pupils were equal and dilated and responded sluggishly to light. Multiple muscle twitches were noted and he was globally hyperreflexic. His ECG showed a broad complex tachycardia.

How should this patient be treated?

- A. D/C cardioversion
 - B. Intravenous Lidocaine
 - C. Intravenous magnesium sulphate
 - D. Intravenous sodium bicarbonate Correct
 - E. Oral activated charcoal
- The history points towards a diagnosis of tricyclic antidepressant (TCA) overdose.
 - Cardiac effects of TCA overdose
 - Hypertension results from the blockade of norepinephrine reuptake and is an early and transient finding. Catecholamines are eventually depleted and in most patients hypertension is mild and self-limiting and is best left untreated.
 - Orthostasis and hypotension are the result of direct myocardial depression, catecholamine depletion, alpha-adrenergic blockade, and arrhythmias. The combination of decreased contractility and vasodilation produce decreased preload and can result in severe and refractory hypotension.
 - Arrhythmias, secondary to blockage or slowing of fast sodium channels (causing a quinidine-like effect) are the most serious consequence of TCA overdose.
 - Prolonged conduction along the His-Purkinje system produces a QRS interval greater than 100 milliseconds. Progression of ECG changes is relatively predictable and related to the severity of the overdose.
 - Mild overdoses produce sinus tachycardia, mostly as a result of anticholinergic effects.
 - More severe overdoses result in prolonged QRS and QTc intervals, followed by a prolonged PR interval, and, finally, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation.
 - Alkalinisation and sodium loading are effective in the treatment of TCA-induced conduction disturbances, ventricular arrhythmias, and hypotension.
 - Sodium bicarbonate attenuates TCA cardiotoxicity via several mechanisms: alkalinisation of blood to a pH of 7.45-7.55 uncouples TCA from myocardial sodium channels; also, additional sodium increases extracellular sodium concentration, thereby improving the gradient across the channel.

St John's Wort

- shown to be as effective as **tricyclic antidepressants** in the treatment of mild-moderate depression

Mechanism:

- thought to be **similar to SSRIs** (although **noradrenaline uptake inhibition** has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs'

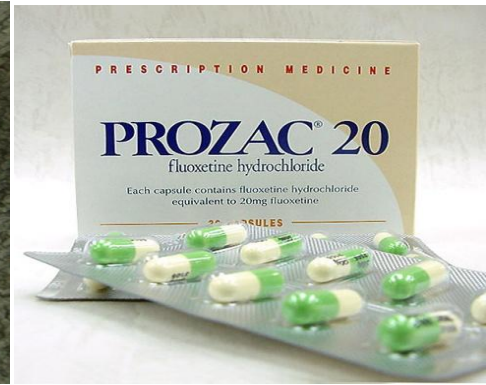
Adverse effects:

- 1) profile in trials similar to placebo
- 2) can cause **serotonin syndrome**
- 3) **Inducer of P450 system**, therefore:
 - ⇒ Decreased levels of drugs such as warfarin, cyclosporine.
 - ⇒ The effectiveness of the COC may also be reduced

Selective serotonin reuptake inhibitors

SSRIs are considered **first-line treatment** for the majority of patients with **depression**.

- 1) **Citalopram** (although $\uparrow$ QT interval) and **fluoxetine** are currently **the preferred ssris**
- 2) **Sertraline** is **useful post myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants
- 3) SSRIs should be used with caution in children and adolescents. **Fluoxetine** is **the drug of choice** when an antidepressant is indicated



Adverse effects:

- 1) **gastrointestinal symptoms:**
 - ☒ the most common side-effect
 - ☒ There is an increased risk of **GIT bleeding**.
 - ☒ A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- 2) patients should be counselled to be vigilant for **increased anxiety** and **agitation** after starting a SSRI
- 3) fluoxetine and paroxetine have a higher propensity for **drug interactions**

Citalopram and the QT interval

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a **warning on the use of citalopram in 2011**
- it advised that citalopram and escitalopram are associated with **dose-dependent QT interval prolongation**
- should not be used in those with:
 - 1) congenital long QT syndrome;
 - 2) known pre-existing QT interval prolongation;
 - 3) or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now:
 - ⇒ 40 mg for adults;
 - ⇒ 20 mg for patients older than 65 years;
 - ⇒ 20 mg for those with hepatic impairment

Interactions:

- 1) **NSAIDs**: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a **proton pump inhibitor**
- 2) **warfarin / heparin**: NICE guidelines recommend avoiding SSRIs and considering mirtazapine (**sertraline** and **citalopram** appear to be the safest antidepressants to prescribe with warfarin {from on examination???}).
- 3) **aspirin**: see above
- 4) **triptans**: avoid SSRIs
 - Following the initiation of antidepressant therapy patients should **normally** be reviewed by a doctor after 2 weeks.
 - For patients **under the age of 30 years** or at **increased risk of suicide** they should be reviewed after 1 week.
 - If a patient makes a good response to antidepressant therapy they should continue on treatment for at least **6 months after remission** as this reduces the risk of relapse.
 - When stopping a SSRI the dose should be gradually reduced **over a 4 week period** (this is not necessary with fluoxetine).
 - **Paroxetine** has a higher incidence of discontinuation symptoms.

Discontinuation symptoms:

- 1) increased mood change
- 2) restlessness
- 3) unsteadiness
- 4) paraesthesia
- 5) difficulty sleeping
- 6) sweating
- 7) Cramping pain, diarrhoea, vomiting

Citalopram	1) the preferred SSRIs 2) prolong the QT interval
Fluoxetine	1) the preferred SSRIs 2) the drug of choice in children and adolescents 3) Can be stopped abruptly 4) fluoxetine and paroxetine have a higher propensity for drug interactions 5) Postnatal depression: fluoxetine is best avoided due to a long half-life
Sertraline	1) useful post myocardial infarction 2) Postnatal depression may be used if symptoms are severe whilst they are secreted in breast milk it is not thought to be harmful to the infant
Paroxetine	1) Postnatal depression may be used if symptoms are severe whilst they are secreted in breast milk it is not thought to be harmful to the infant 2) treatments for PTSD 3) fluoxetine and paroxetine have a higher propensity for drug interactions 4) Paroxetine has a higher incidence of discontinuation symptoms
Mirtazapine	1) NICE guidelines recommend avoiding SSRIs and considering mirtazapine if the pt is taking warfarin or heparin 2) treatments for PTSD

sertraline and **citalopram** appear to be the safest antidepressants to prescribe with warfarin

Mirtazapine: العلم فقط

- Tetracyclic structure different from SSRIs, TCAs and MAOIs;
- through its central presynaptic alpha2-adrenergic antagonist effects, stimulates norepinephrine and serotonin release;
- potent antagonist of 5-HT2 and 5-HT3 serotonin and histamine receptors; is a moderate alpha1 adrenergic and muscarinic antagonist

Serotonin syndrome

Causes

- monoamine oxidase inhibitors MAOI
- SSRIs (سؤال الامتحان) plus sumatriptan)
- Ecstasy, amphetamines

Features:

- 1) altered **mental** state e.g. anxiety, agitation, hypomania, confusion, coma
- 2) **neuromuscular excitation** e.g. hyperreflexia, tremor, myoclonus, incoordination, seizures,
- 3) **autonomic excitation** (e.g. hyperthermia, HTN, tachycardia, salivation)

Treatment:

- ☒ Treatment is supportive and involves removing the precipitating drugs, controlling agitation and controlling hyperthermia.
- ☒ administering serotonin antagonists (**cypheptadine** or methysergide)

Antipsychotics

- Antipsychotics act as **dopamine D2 receptor antagonists**,
 - ☒ blocking dopaminergic transmission in the **mesolimbic pathways**
- Conventional antipsychotics are associated with problematic **extrapyramidal side-effects** which has led to the development of atypical antipsychotics such as clozapine

Examples of Conventional antipsychotics:

- **haloperidol**
- **Chlorpromazine**
- **Phenothiazines**

Extrapyramidal side-effects

- 1) **Parkinsonism**
- 2) **acute dystonia** (e.g. torticollis, oculogyric crisis)
- 3) **akathisia** (severe restlessness)
- 4) **tardive dyskinesia:**
 - ☒ Late onset of choreoathetoid movements, abnormal, involuntary,
 - ☒ may occur in 40% of patients, may be irreversible,
 - ☒ most common is chewing and pouting of jaw

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- 1) increased risk of **stroke**
- 2) increased risk of **venous thromboembolism**

Other side-effects

- 1) antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- 2) sedation, weight gain
- 3) **raised prolactin:** galactorrhoea
- 4) **SIADH**
- 5) **impaired glucose tolerance,**
- 6) neuroleptic malignant syndrome: pyrexia, muscle stiffness
- 7) reduced **seizure** threshold (greater with atypicals)
- 8) prolonged QT interval (particularly haloperidol)

Phenothiazines

- Have antiemetic and antipsychotic properties, making them the medication of choice for acute porphyria episodes.
- Can be used in migraine

Atypical Antipsychotics

- Should be used **first-line** in patients with **schizophrenia**, according to 2005 NICE guidelines.
- The main advantage of the atypical agents is a **significant reduction** in extra-pyramidal side-effects.

Adverse effects of atypical antipsychotics:

- 1) **weight gain**
- 2) clozapine is associated with **agranulocytosis**

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- 1) increased risk of **stroke** (especially olanzapine and risperidone)
- 2) increased risk of **venous thromboembolism**

Examples of atypical antipsychotics

- clozapine
- olanzapine
- quetiapine
- risperidone
- amisulpride

Clozapine:

- One of the first atypical agents to be developed
- Carries a significant risk of **agranulocytosis**
- Full blood count monitoring is therefore essential during treatment.
- For this reason clozapine should only be used in patients resistant to other antipsychotic medication

Adverse effects of clozapine:

- 1) **Agranulocytosis** (1%), **neutropaenia** (3%)
- 2) **reduced seizure threshold**
 - ☒ Can induce seizures in up to 3% of patients
- 3) **Atypical antipsychotics** such as clozapine / olanzapine / risperidone have been associated with **hyperglycaemia** and **insulin resistance**.
 - ☒ The mechanism remains obscure,
 - ☒ But withdrawal of the medication may produce resolution of the diabetes.

Neuroleptic Malignant Syndrome

- a rare but dangerous condition seen in patients taking antipsychotic medication
- Caused by a **sudden reduction in dopamine activity**, either from blockade of dopamine receptors or withdrawal of dopaminergic agents.
- It carries a mortality of up to 10% and can also occur with atypical antipsychotics.
- It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

Features:

- more common in young male patients
- Onset usually in first 10 days of treatment or after increasing dose but it can occur at any time during the treatment with antipsychotic medications.
- Concomitant treatment with **lithium** or **anticholinergics** may increase the risk of NMS.

- 1) **Fever**
- 2) **rigidity**
- 3) **Altered mental status**
- 4) **Autonomic dysfunction**
- 5) tachycardia
- 6) raised creatine kinase:
 - ☒ present in most cases
 - ☒ always elevated ($>1000 \text{ IU/L}^{-1}$)
 - ☒ reflecting myonecrosis secondary to intense muscle contracture
- 7) leukocytosis may also be seen

Management:

- 1) stop antipsychotic
- 2) IV fluids to prevent renal failure
- 3) Reduction of body temperature with antipyretics.
- 4) **dantrolene** may be useful in selected cases
- 5) **bromocriptine**, **dopamine agonist**, may also be used

dantrolene thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum

- Serotonin syndrome is a differential diagnosis for NMS but the two can be easily distinguished on thorough history and examination.
- NMS develops over days and weeks, whereas serotonin syndrome can develop over 24 hrs.
- Serotonin syndrome develops neuromuscular hyperreactivity, (myoclonus, tremors, hyperreflexia) whereas NMS involves sluggish neuromuscular response (bradyreflexia, rigidity).
- Hyperreflexia and myoclonus are rare in NMS.
- Also resolution of NMS takes up to nine days whereas (usually) it takes less than 24 hours in serotonin syndrome.
- Hyperthermia, muscle rigidity, leukocytosis, elevated CK, altered hepatic function and metabolic acidosis are common to severe cases in both conditions

Malignant hyperthermia

- A condition often seen following administration of **anaesthetic agents**
- characterised by **hyperpyrexia** and **muscle rigidity**
- cause by **excessive release of Ca²⁺** from the **sarcoplasmic reticulum** of skeletal muscle
- associated with defects in a gene on **chromosome 19** encoding the **ryanodine receptor**, which controls Ca²⁺ release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

Causative agents:

- 1) halothane
- 2) suxamethonium
- 3) other drugs: antipsychotics (neuroleptic malignant syndrome)

Investigations:

- 1) CK raised
- 2) contracture tests with halothane and caffeine

Management:

- **dantrolene**: prevents Ca²⁺ release from the sarcoplasmic reticulum

Acute dystonic-dyskinetic reactions

- Mostly occur in children and young adults and
- About 70% of cases are female.
- It occurs more commonly when excess of the recommended dose of **metoclopramide** is administered.

Symptoms include:

- 1) oculogyric crisis
 - 2) opisthotonus
 - 3) torticollis
 - 4) trismus, and
 - 5) Tetanus-like reactions.
- A blue discolouration of the tongue has also been described.
 - The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.

Management:

- ☒ Generally self-limiting,
- ☒ the reaction can be reversed by:
 - 1) Anticholinergic such as **benzatropine** or **procyclidine** or
 - 2) Antihistamine such as **diphenhydramine**.

Oculogyric crisis (acute dystonia)

An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions

Features:

- restlessness, agitation, trismus, opisthotonus, torticollis
- involuntary upward deviation of the eyes

Causes:

- 1) **Antipsychotics**: phenothiazines: prochlorperazine, chlorpromazine ,haloperidol
- 2) metoclopramide
- 3) postencephalitic Parkinson's disease

Management

- ☒ **Anticholinergic**: **procyclidine**, **beztropine**...or
- ☒ **Antihistaminic**: **diphenhydramines**

Alcohol withdrawal

Mechanism:

- chronic alcohol consumption:
 - 1) enhances **GABA mediated inhibition** in the CNS (similar to benzodiazepines) and
 - 2) inhibits **NMDA-type glutamate receptors**
- alcohol withdrawal is thought to lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

Features:

- 1) symptoms start at **6-12 hours**
- 2) peak incidence of **seizures** at **36 hours**
- 3) Peak incidence of **delirium tremens** is at **72 hours**:
 - ☒ **Visual hallucinations** مهمة جدا
 - ☒ **autonomic instability** (tachycardia, hypertension, and pyrexia),
 - ☒ **Sweating, tremors**
 - ☒ **obtundation** تلبد الإحساس and **confusion**
 - ☒ **Agitation**

(Hallucinations is not a feature of opiate withdrawal).

Management:

- 1) **Benzodiazepines**
- 2) **carbamazepine** also effective in treatment of alcohol withdrawal
- 3) phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

Alcohol - problem drinking management

Nutritional support

- SIGN recommends alcoholic patients should receive **oral thiamine** if their 'diet may be deficient'

Drugs used

- 1) **Benzodiazepines** for **acute withdrawal**
- 2) **Disulfram**:
 - **Promotes abstinence**
 - alcohol intake causes severe reaction due to inhibition of **acetaldehyde dehydrogenase**
 - Patients should be aware that even small amounts of alcohol (e.g. in perfumes, foods, mouthwashes) can produce severe symptoms.
 - Contraindications include **IHD** and **psychosis**
- 3) **Acamprosate**:
 - **reduces craving**,
 - known to be a weak antagonist of NMDA receptors,
 - improves abstinence in placebo controlled trials

Ethylene glycol toxicity

Ethylene glycol is a type of alcohol used as a **coolant** or **antifreeze**

Features of toxicity are divided into 3 stages:

Stage 1: symptoms similar to alcohol intoxication: **confusion**, **slurred speech**, **dizziness**

Stage 2:

- **metabolic acidosis** with high anion gap and high osmolar gap
- Also **tachycardia**, **hypertension**

Stage 3: **acute renal failure**

Management has changed in recent times

1) **Fomepizole**:

- an inhibitor of alcohol dehydrogenase
- now used **first-line** in preference to ethanol

2) **Ethanol**:

- has been used for many years
- works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
- this limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning

3) **Haemodialysis** also has a role in refractory cases

Methanol poisoning

- Early signs of toxicity are due to **methanol**;
- Later signs are due to its metabolite, **formic acid**.
- **Early signs include**:
 - 1) Nausea
 - 2) Vomiting
 - 3) Headache, and
 - 4) Confusion.
- **Formic acid** later produces:
 - 1) a metabolic acidosis and
 - 2) Retinal injury, optic neuropathy, blindness

Diagnosis: can be made early by measurement of **serum methanol** and **serum formate** levels.

Treatment is aimed at:

- 1) Elimination of formic acid (**alkaline diuresis** or **haemodialysis**)
 - 2) Correction of acidosis with **intravenous bicarbonate** and
 - 3) Preventing metabolism of methanol to formic acid by administration of intravenous **fomepizole** or **ethanol**.
- The recommended treatment includes **fomepizole** which is an **inhibitor of alcohol dehydrogenase**.
 - If this is not available or cost prohibits the use, then ethanol is recommended.

Benzodiazepines

- Benzodiazepines enhance the effect of the inhibitory neurotransmitter **gamma-aminobutyric acid (GABA)** by increasing the frequency of chloride channels.
- **They therefore are used for a variety of purposes:**
 - 1) sedation
 - 2) hypnotic
 - 3) anxiolytic
 - 4) anticonvulsant
 - 5) muscle relaxant
- Patients commonly develop a **tolerance** and **dependence** to benzodiazepines and care should therefore be exercised on prescribing these drugs.
- The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a **short period** of time (**2-4 weeks**).
- The BNF gives advice on how to withdraw a benzodiazepine.
- The dose should be withdrawn in steps of about **1/8** (range 1/10 to 1/4) of the daily dose **every fortnight** كل أسبوعين
- **A suggested protocol for patients experiencing difficulty is given:**
 - 1) **switch** patients **to** the equivalent dose of **diazepam**
 - 2) reduce dose of diazepam every 2-3 weeks in steps of **2 or 2.5 mg**
 - 3) time needed for withdrawal can vary from 4 weeks to a year or more

Benzodiazepine withdrawal syndrome

- a condition very similar to alcohol withdrawal syndrome occurs If patients withdraw too quickly from benzodiazepines
- This may occur up to **3 weeks** after stopping a long-acting drug.

Features include:

- 1) insomnia
- 2) irritability
- 3) anxiety
- 4) tremor
- 5) perspiration عرق
- 6) loss of appetite
- 7) tinnitus
- 8) perceptual disturbances اضطرابات إدراكية
- 9) seizures

Opioid misuse

- Opioids are substances which bind to opioid receptors.
- This includes both:
 - ☒ **Naturally occurring opiates** such as **morphine** and
 - ☒ **Synthetic opioids** such as **buprenorphine** and **methadone**.
- Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution (rapid confusion).

Features of opioid misuse:

- 1) rhinorrhoea, watering eyes, pinpoint pupils
- 2) drowsiness, sedation, yawning
- 3) nausea, vomiting, constipation
- 4) needle track marks
- 5) rare symptoms of neurotoxicity (for example, hallucinations, myoclonus and delirium)

Complications of opioid misuse:

- 1) viral infection secondary to sharing needles: HIV, hepatitis B & C
- 2) bacterial infection secondary to injection: infective endocarditis, septic arthritis, septicaemia, necrotising fasciitis
- 3) venous thromboembolism
- 4) Overdose may lead to respiratory depression and death
- 5) psychological problems: craving
- 6) social problems: crime, prostitution, homelessness

Emergency management of opioid overdose:

- ☒ IV or IM **naloxone**: has a rapid onset and relatively short duration of action

Harm reduction interventions may include:

- 1) needle exchange
- 2) offering testing for HIV, hepatitis B & C

Management of opioid dependence:

- 1) patients are usually managed by specialist drug dependence clinics although some GPs with a specialist interest offer similar services
- 2) patients may be offered **maintenance therapy** or **detoxification**
- 3) NICE recommend **methadone** or **buprenorphine** as the **first-line** treatment in **opioid detoxification**
- 4) compliance is monitored using **urinalysis**
- 5) detoxification should normally last up to **4 weeks** in an inpatient/residential setting and up to **12 weeks** in the community

Naloxone Competitive opioid antagonist

Onset: 2 min (IV); 2-5 min (IM/SC)

Duration: Depends on route of administration; generally 1-2 hr

Half-life: 30-90 min (adults); 3-4 hr (neonates) Excretion: Urine

Opioid Withdrawal

Features:

- Sympathetic activity
- agitated and confused,
- tachycardia, hyperthermia, HTN,
- sweating, salivation,
- dilated pupils,
- **brisk reflexes** with **extensor plantar responses**

TTT:

☒ Tapering doses of **methadone** is the treatment of choice

(Hallucinations is not a feature of opiate withdrawal).

Cocaine

- Cocaine is an alkaloid derived from the coca plant.
- It is widely used as a recreational stimulant.
- The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem.
- This increase has made cocaine a favourite topic of question writers.

Mechanism of action:

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

Adverse Effects: Cocaine has predominantly sympathetic effects

Cardiovascular effects:

- 1) myocardial infarction due to coronary spasm
- 2) aortic dissection
- 3) both tachycardia and bradycardia may occur
- 4) hypertension
- 5) QRS widening and QT prolongation

Neurological effects:

- 1) Mydriasis
- 2) seizures
- 3) hypertonia
- 4) hyperreflexia

Psychiatric effects:

- 1) agitation
- 2) psychosis
- 3) hallucinations

Others:

- 1) hyperthermia
- 2) metabolic acidosis
- 3) rhabdomyolysis

Management of cocaine toxicity

☒ in general **benzodiazepines** are generally **first-line** for most cocaine related problems

- 1) HTN: → benzodiazepines + sodium nitroprusside
- 2) Chest pain: → benzodiazepines + glyceryl trinitrate.
- 3) If myocardial infarction develops then primary PCI

The use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue.

The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (**due to the risk of unopposed alpha-mediated coronary vasospasm**) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

- Cocaine has predominantly sympathetic effects due to the central inhibition of catecholamine and serotonin reuptake.
- Agitation, seizures and hypertension are best treated with benzodiazepines (such as midazolam) initially. Beta blockers are contraindicated as they can cause unopposed alpha activity and worsen hypertension.
- Calcium channel blockers (such as nifedipine) can be used as a second line treatment for hypertension if benzodiazepines are ineffective.
- Clonidine or dexmedetomidine are centrally acting alpha-2 agonists and can be used to treat anxiety and hypertension with a single agent. Dexmedetomidine has only recently become available in the UK.
- Labetolol does not abolish coronary artery spasm and is therefore not first line treatment.

Ecstasy

- Ecstasy (**MDMA**, 3, 4-Methylene-dioxy-methamphetamine)
- Its use became popular in the 1990's during the emergence of dance music culture

Clinical features:

- 1) Mydriasis, agitation, anxiety, ataxia, confusion
- 2) cardiovascular: tachycardia, HTN
- 3) hypon**atraemia**
- 4) hyper**thermia**
- 5) Hyper**kalaemia**
- 6) **rhabdomyolysis**
- 7) **Acute renal failure**
- 8) **Hepatocellular necrosis**
- 9) **DIC**
- 10) **ARDS**

Management:

- ☒ Supportive (no antidote)
- ☒ **dantrolene** may be used for hyperthermia if simple measures fail

Hemiballismus: the lesion is in the contralateral subthalamic nucleus

TTT: **Tetrabenazine**

Corticosteroids

Steroid doses

Equivalence:

- 1 mg prednisolone = 4 mg hydrocortisone
- 1 mg dexamethasone = 7 mg prednisolone = 28 mg hydrocortisone
- Corticosteroids are amongst the most commonly prescribed therapies in clinical practice.
- They are used both systemically (oral or intravenous) or locally (creams, inhalers, eye drops, intraarticular).
- They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity	Glucocorticoid activity, high mineralocorticoid activity	Predominant glucocorticoid activity, low mineralocorticoid activity	Very high glucocorticoid activity, minimal mineralocorticoid activity
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects:

- Numerous & represent the single greatest limitation on their use.
- more common with systemic and prolonged therapy

Glucocorticoid side-effects:

- 1) endocrine:
 - ⇒ impaired glucose regulation,
 - ⇒ increased appetite/weight gain,
 - ⇒ hyperlipidaemia
 - ⇒ hirsutism,
 - ⇒ Cushing's syndrome: moon face, buffalo hump, striae
- 2) musculoskeletal:
 - ⇒ osteoporosis,
 - ⇒ proximal myopathy,
 - ⇒ avascular necrosis of the femoral head
- 3) immunosuppression: increased susceptibility to severe infection, reactivation of TB
- 4) psychiatric: insomnia, mania, depression, psychosis
- 5) gastrointestinal: peptic ulceration, acute pancreatitis
- 6) glaucoma, cataracts
- 7) suppression of growth in children
- 8) intracranial hypertension

Mineralocorticoid side-effects:

- fluid retention
- hypertension

Selected points on the use of corticosteroids: هام جدا

- 1) Patients on long-term steroids
 - ⇒ should have their **doses doubled** during intercurrent illness
 - ⇒ if severe illness **IV hydrocortisone 50-100mg / 6hrs** (**Mineralocorticoid no dose change**)
- 2) The BNF suggests gradual withdrawal of systemic corticosteroids if patients: received > 40mg prednisolone daily for > one week, received > 3 weeks treatment or recently received repeated courses.

Azathioprine

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that **inhibits purine synthesis**.
- Thiopurine methyltransferase inactivate mercaptopurine
- Thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used (decrease the dose by 25%)

Adverse effects include:

- 1) bone marrow depression
- 2) nausea/vomiting
- 3) pancreatitis

Cyclosporine (CNI)

Calcineurin Inhibitor

- An immunosuppressant which decreases **clonal proliferation of T cells** by reducing **IL-2 release**.
- It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a **phosphatase** that activates various transcription factors in **T cells**

Adverse effects: (note how everything is increased - fluid, BP, K⁺, hair, gums, glucose)

- 1) Nephrotoxicity (can cause HUS)
- 2) hepatotoxicity
- 3) fluid retention
- 4) hypertension
- 5) hyperkalaemia
- 6) **hypertrichosis** (increase body hair {non androgen related })
- 7) gingival hyperplasia
- 8) tremor (common)
- 9) impaired glucose tolerance
- 10) hyperlipidaemia
- 11) increased susceptibility to severe infection

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

Indications:

- 1) following organ transplantation
- 2) rheumatoid arthritis
- 3) psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- 4) ulcerative colitis
- 5) pure red cell aplasia

Tacrolimus

- Tacrolimus is a **macrolide** used as an immunosuppressant to prevent transplant rejection.
- It has a very similar action to cyclosporine
- The action of tacrolimus differs in that it binds to a protein called **FKBP** rather than cyclophilin
- Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less. However, **nephrotoxicity** and **impaired glucose tolerance** is more common

Haemodialysis in overdose

Drugs that can be **cleared** with haemodialysis - mnemonic: BLAST

- 1) Barbiturate
- 2) Lithium
- 3) Alcohol (including methanol, ethylene glycol)
- 4) Salicylates
- 5) Theophyllines (charcoal haemoperfusion is preferable)

Drugs which **cannot be cleared** with haemodialysis include

- 1) Tricyclics TCAs
- 2) Benzodiazepines BZD
- 3) dextropropoxyphene (Co-proxamol)
- 4) digoxin
- 5) beta-blockers BB

Therapeutic drug monitoring

Lithium

- range = 0.4 - 1.5 mmol/l
- take 12 hrs post-dose
- Level > 4 → Haemodialysis

Digoxin

- at least 6 hrs post-dose

Phenytoin

- trough levels immediately before dose

Ciclosporin

- trough levels immediately before dose

Paracetamol overdose

Risk factors:

The following groups of patients are at an increased risk of developing hepatotoxicity following a paracetamol overdose:

- 1) patients taking **liver enzyme-inducing drugs**:
 - ☒ Rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort
 - 2) **malnourished patients**
e.g anorexia or bulimia, cystic fibrosis, HCV, alcoholism, HIV
 - 3) patients who **have not eaten** for a few days
- ☒ A dose of **> 150 mg/kg** is considered to be toxic
- ☒ Toxicity occurs at a lower concentration if the patient is thought to be in high risk group.

Paracetamol overdose - high risk if chronic alcohol, HIV, anorexia or P450 inducers
Anorexic patients have depleted glutathione stores and are therefore more at risk from liver injury

Metabolic pathways:

- 1) The liver normally **conjugates** paracetamol with glucuronic acid/sulphate.
 - 2) During an overdose the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*.
 - 3) This produces a toxic metabolite (**N-acetyl-p-benzoquinone imine**) NAPQI
 - 4) Normally **glutathione** acts as a defence mechanism by conjugating with the toxin forming the non-toxic **mercapturic acid**.
 - 5) If glutathione stores run-out, the toxin forms covalent bonds with cell proteins, denaturing them and leading to **cell death**.
 - 6) This occurs not only in **hepatocytes** but also in the **renal tubules**
 - 7) **N-acetyl cysteine** is used in the management of paracetamol overdose as it is a **precursor of glutathione** and hence can increase hepatic glutathione production
- *this explains why there is a lower threshold for treating patients who take P450 inducers e.g. phenytoin or rifampicin

Management:

- ☒ All patients are treated the same regardless of risk factors for hepatotoxicity.
- ☒ The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

The essentials of management are:

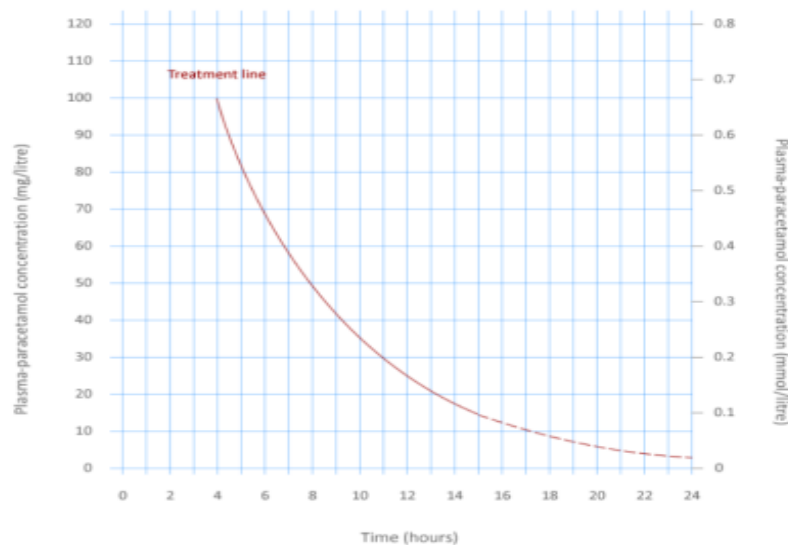
- 1) Check paracetamol level four hours after ingestion, check levels against the Rumack-Matthew nomogram.
- 2) **Gastric lavage** if large dose ingested (**more than 7.5 g**) and/or presenting **within eight hours** of ingestion; consider **oral charcoal**.
- 3) Give **N-acetylcysteine** or **methionine**.
- 4) Hourly BMs monitored.
- 5) Check INR 12 hourly.

☒ Acetylcysteine should be given if:

- 1) there is a staggered overdose* or there is doubt over the time of paracetamol ingestion, regardless of the plasma paracetamol concentration; or
- 2) the plasma paracetamol concentration is on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours, regardless of risk factors of hepatotoxicity

☒ Acetylcysteine is now infused **over 1 hour** (rather than the previous 15 minutes) to reduce the number of adverse effects.

*an overdose is considered staggered if all the tablets were not taken within 1 hour



King's College Hospital criteria for liver transplantation
(paracetamol liver failure)

- ☒ Arterial pH < 7.3, 24 hours after ingestion
- ☒ or all of the following:
- prothrombin time > 100 seconds
 - creatinine > 300 $\mu\text{mol/l}$
 - grade III or IV encephalopathy

Signs associated with poor prognosis (and indicating need for transfer to a liver unit) include:

- INR greater than 2.0 within 48 hours or greater than 3.5 within 72 hours of ingestion
 - Creatinine greater than 200 $\mu\text{mol/L}$
 - Blood pH less than 7.3
 - Signs of encephalopathy
 - Hypotension (SBP less than 80 mmHg)
 - Hypoglycemia.
- ☒ Liver enzymes are a poor marker of the degree of hepatocellular damage;
- ☒ Synthetic function (as determined by INR or PT) is the best indicator.

Criteria for liver transplant in fulminant failure in non-paracetamol cases include:

- ✗ INR greater than 6.7 or prothrombin time greater than 100 seconds, or**
- ✗ any three of the following:**
 - Aetiology that is not due to hepatitis A, hepatitis B or a drug reaction
 - Age less than 10 years or more than 40 years
 - Jaundice more than seven days before encephalopathy
 - INR greater than 4 or prothrombin time greater than 50 seconds, and
 - Bilirubin greater than 300 $\mu\text{mol/L}$.

Salicylate overdose

- A key concept for the exam is to understand that salicylate overdose leads to a **mixed respiratory alkalosis** and **metabolic acidosis**.
 - ☒ Early stimulation of the respiratory centre leads to a respiratory alkalosis
 - ☒ whilst later the direct acid effects of salicylates combined with acute renal failure may lead to an acidosis
- In children **metabolic acidosis** tends to predominate

Features:

- 1) hyperventilation (centrally stimulates respiration)
- 2) **tinnitus** is characteristic and salicylate ototoxicity may produce deafness
- 3) lethargy
- 4) sweating, pyrexia
- 5) nausea/vomiting
- 6) hyperglycaemia and hypoglycaemia
- 7) **seizures**
- 8) **coma**

Treatment:

- 1) The initial treatment especially of this patient should include the administration of **activated charcoal** and repeated as bezoars may form resulting in delayed absorption of salicylate. This should continue until salicylate levels have peaked.
- 2) **Gastric lavage** is useful if the ingestion is known to have occurred **within one hour** but the airway should be protected during the procedure.
- 3) **urinary alkalization**
 - The patient should then be **rehydrated and the urine alkalinised** to promote urinary excretion. This is achieved by giving an infusion of 1.25% or 8.4% sodium bicarbonate.
 - The ionisation of a weak acid, such as salicylic acid is increased in an alkaline environment.
 - The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold.
- 4) **Haemodialysis:**

Indications for haemodialysis in salicylate overdose

- 1) serum concentration **> 700mg/L**
- 2) metabolic acidosis resistant to treatment
- 3) acute renal failure
- 4) pulmonary oedema
- 5) seizures
- 6) coma

***salicylates cause the uncoupling of oxidative phosphorylation leading to decreased ATP production, increased O₂ consumption and increased CO₂ and heat production**

A 25-year-old woman is admitted to the Emergency department with a suspected overdose of aspirin. The patient has been vomiting and complains of tinnitus. On examination she is sweating profusely, clinically dehydrated and restless. Her vital signs are: temperature 38.5°C, pulse 120 regular, blood pressure 140/85 mmHg, respiratory rate 25 breaths per minute, Glasgow coma score of 12 and oxygen saturation 95% on air. It is thought that the aspirin was ingested eight hours ago

pH	7.25	(7.35-7.45)
PaCO ₂	20 mmHg	(38-42)
PaO ₂	102 mmHg	(75-100)
BE	+8	(-3 to +3)
Bicarbonate	22 mEq/L	(22-28)
SpO ₂	96%	
Glucose	13 mmol/L	(3.5-5.5)
Salicylate levels	601 mg/L	

Which one of the following is the most appropriate initial clinical intervention in this case?

☐	Activated charcoal
☒	Alkalise the urine Correct
☐	Gastric lavage
☐	Forced diuresis
☐	Haemodialysis

- The clinical picture of this patient is consistent with a moderate overdose of aspirin.
- There is no specific antidote to ingested salicylates.
- The management of a poisoning is supportive with measures to prevent further absorption from the gastrointestinal tract and enhance excretion.
- The initial treatment especially of this patient should include the administration of **activated charcoal** and repeated as bezoars may form resulting in delayed absorption of salicylate. This should continue until salicylate levels have peaked.
- **Gastric lavage** is useful if the ingestion is known to have occurred **within one hour** but the airway should be protected during the procedure.

- The patient should then be **rehydrated and the urine alkalinised** to promote urinary excretion. This is achieved by giving an infusion of 1.25% or 8.4% sodium bicarbonate.
- The ionisation of a weak acid, such as salicylic acid is increased in an alkaline environment.
- The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold.
- A forced diuresis alone is not recommended as it can lead to severe electrolyte disturbance and pulmonary or cerebral oedema.
- Severe cases of salicylate poisoning where plasma levels of salicylate are **high >800 mg/L**, severe metabolic acidosis, acute kidney injury or have neurological impairment (coma, hallucinations or seizures) may require early **haemodialysis**.

Answer B

Lead poisoning

- Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

Features:

- 1) abdominal pain, constipation
- 2) fatigue, Anemia, arthralgia, renal failure
- 3) peripheral neuropathy (mainly motor)
- 4) blue lines on gum margin (only 20% of adult patients, very rare in children)

Mild cases of lead poisoning are associated with:

- Lethargy
- Anorexia
- Abdominal discomfort, and
- Arthralgia.

Moderate cases exhibit:

- Anaemia
- Headache
- Abdominal cramps
- A gingival blue lead line, and
- Peripheral motor neuropathy.

In severe cases there are:

- Convulsions
- Coma
- Encephalopathy
- Renal failure.

Blood tests reveal:

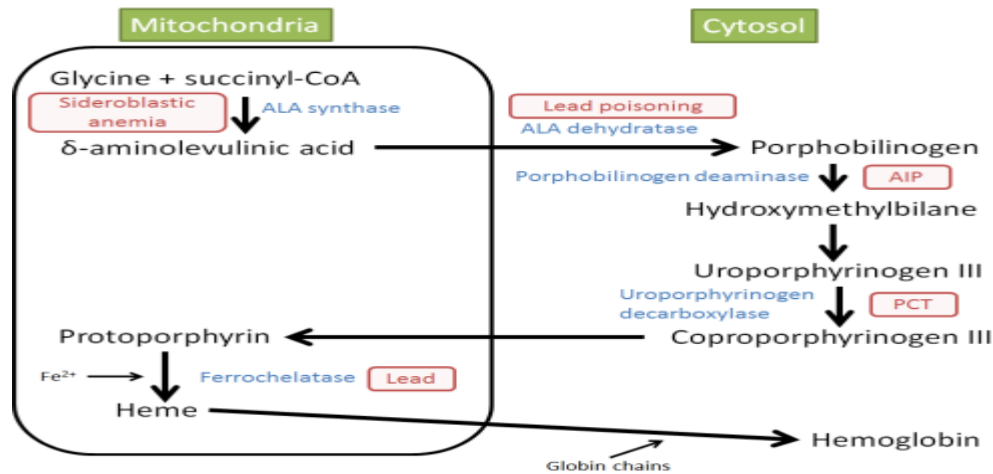
- ☒ a hypochromic, microcytic anaemia and
- ☒ Basophilic stippling of red cells.

Investigations:

- 1) The blood lead level is usually used for diagnosis. Levels > 10 mcg/dl are considered significant
- 2) Full blood count: microcytic anaemia.
- 3) Blood film shows red cell: basophilic stippling and clover-leaf morphology
- 4) raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- 5) urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management: various chelating agents are currently used:

- 1) dimercaptosuccinic acid (DMSA), succimer
- 2) Dimercaprol
- 3) D-penicillamine
- 4) EDTA



porphobilinogen deAminase ---> AIP
 uroporphyrinogen deCarboxylase ----> PCT

Arsenic poisoning

- The combination of:
 - ☒ Mixed sensorimotor polyneuropathy
 - ☒ in the presence of possible exposure to pesticides
 - ☒ In a farmer
 Suggests diagnosis of chronic arsenic poisoning
- The transverse white lines on the finger nails are Mees' lines.
- Lead poisoning gives a predominantly motor neuropathy.

Magnesium toxicity

Signs of hypermagnesaemia include:

- Nausea
- Vasodilatation, and
- Hypotension (myocardial depression + vasodilatation).

In severe cases it can also include:

- Drowsiness
- Double vision
- Loss of deep tendon reflexes
- Respiratory depression
- Bradycardia
- Coma, and
- Cardiac arrest.

Magnesium toxicity is more common when intravenous magnesium is given in absence of hypomagnesaemia such as pre-eclampsia and is exacerbated in the presence of renal failure.

Mercury poisoning

Features

- 1) paraesthesia
- 2) irritability
- 3) visual field defects
- 4) hearing loss
- 5) renal tubular acidosis RTA

Acute iron poisoning

- Typically presents with gastrointestinal symptoms - vomiting, diarrhoea, abdominal pain and gastrointestinal haemorrhage are typical of a toxic iron overdose.
- Following this initial presentation symptoms typically abate until the development of severe metabolic acidosis, cardiovascular complications and CNS depression.
- Patients who survive this stage of iron toxicity go on to develop hepatic dysfunction.
- Resolution is characterised by scarring of the gastrointestinal tract with stricture formation and possible gastrointestinal obstruction.
- Iron tablets are radiopaque and thus may be visualised on plain films or CT.

Lithium

- Lithium is mood stabilising drug used most commonly prophylactically in **bipolar disorder** but also as an adjunct in **refractory depression**.
- It has a very narrow therapeutic range (0.5-1.5 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:

- 1) interferes with inositol triphosphate formation
- 2) interferes with cAMP formation

Adverse effects:

- 1) nausea/vomiting, **diarrhoea**
- 2) polyuria (secondary to **nephrogenic DI**)
- 3) weight gain
- 4) thyroid enlargement, may lead to **hypothyroidism**
- 5) **fine tremor**
- 6) ECG: T wave flattening/inversion
- 7) **Ebstein's anomaly** may be caused by exposure to **lithium** in-utero

Monitoring of patients on lithium therapy

Inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic

- 1) Lithium blood level should 'normally' be checked **every 3 months**.
Levels should be taken **12 hours post-dose**
- 2) thyroid and renal function should be checked **every 6 months**
- 3) patients should be issued with an information booklet, alert card and record book

Lithium toxicity

- Lithium toxicity generally occurs following concentrations $> 1.5 \text{ mmol/L}$.
- Toxicity may be precipitated by:
 - 1) dehydration, diuretics (especially bendroflumethiazide)
 - 2) ACE inhibitors, NSAIDs
 - 3) renal failure,
 - 4) Metronidazole

Features of toxicity: رعشة ... تشنجات ... هذيان غيبوبة

- 1) coarse tremor (a fine tremor is seen in therapeutic levels)
- 2) seizure
- 3) acute confusion, coma
- 4) may cause Rhabdomyolysis

Management:

- 1) mild-moderate toxicity may respond to volume resuscitation **with normal saline**
- 2) **Haemodialysis** may be needed in severe toxicity (lithium level of greater than **4 mmol/L** or features of **CNS** toxicity or **cardiac instability** are indications for haemodialysis).
- 3) **Sodium bicarbonate** is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion
- 4) **Whole bowel irrigation** should be considered in adults who have ingested a slow release preparation of lithium of greater than **4 g**.

Methaemoglobinaemia

- Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe²⁺ (ferrous iron) to Fe³⁺ (ferric iron).
- This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin.
- There is tissue hypoxia as Fe³⁺ cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital

- 1) haemoglobin chain variants: HbM, HbH
- 2) NADH methaemoglobin reductase deficiency

Acquired

- 1) drugs:
 1. phenacetin
 2. sulphonamides,
 3. nitrates, sodium nitroprusside,
 4. primaquine, procaine, lidocaine, benzocaine
 5. dapsone
- 2) chemicals: aniline dyes

Features:

- 1) 'chocolate' cyanosis
- 2) normal pO₂ but decreased oxygen saturation مميزة
- 3) dyspnoea, anxiety, headache
- 4) severe: acidosis, arrhythmias, seizures, coma

Management:

- 1) NADH – methaemoglobin reductase deficiency: ascorbic acid
- 2) If acquired: IV methylene blue
- 3) hyperbaric O₂, RBCS Tx, Exchange transfusion or dialysis

Carbon monoxide poisoning

- Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia.
- There are approximately 50 per year deaths from accidental CO poisoning in the UK
- Questions may hint at badly maintained housing e.g. student houses, Fumes of cleaning fluids & paint remover contain methylene chloride (dichloromethane), converted into CO.

Features of carbon monoxide toxicity:

- 1) headache: 90% of cases
- 2) nausea and vomiting: 50%
- 3) vertigo: 50%
- 4) confusion: 30%
- 5) subjective weakness: 20%
- 6) severe toxicity:
 - **Pink** skin and mucosa,
 - **Arrhythmias**,
 - **hyperpyrexia, extrapyramidal** features,
 - coma, death

Typical carboxyhaemoglobin levels:

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

Management:

- 1) 100% oxygen
- 2) hyperbaric oxygen

Indications for hyperbaric oxygen:

- 1) loss of consciousness at any point
- 2) neurological signs other than headache
- 3) myocardial ischaemia or arrhythmia
- 4) pregnancy

Cyanide Poisoning

- Cyanide may be used in **insecticides**, **photograph development** and the **production of certain metals**.
- Toxicity results from **reversible inhibition of cellular oxidising enzymes**

Presentation:

- 1) 'classical' features: **brick-red skin**, smell of **bitter almonds** اللوز المر
- 2) **acute**:
 - ⇒ hypoxia, hypotension, headache, confusion
- 3) **chronic**:
 - ⇒ ataxia, peripheral neuropathy, dermatitis

Management:

- 1) supportive measures: **100% oxygen**
- 2) definitive:
 - ☒ **hydroxocobalamin (IV)**, also
 - ☒ combination of **amyl nitrite** (inhaled), **sodium nitrite (IV)**, and **sodium thiosulfate IV**

- Cyanide causes the inhibition of the enzyme cytochrome oxidase c which is an essential part of the mitochondrial electron transfer chain (ETC).
- It therefore interferes with the basic process of cellular respiration, preventing the formation of ATP and causing rapid cell death.
- Arsenic causes inhibition of the enzyme pyruvate dehydrogenase which is necessary for the conversion of pyruvate to acetyl CoA. This also interferes with the basic process of cellular respiration, as pyruvate formed during glycolysis cannot be changed to acetyl CoA to enter the Krebs cycle.
- Unfortunately, many agents also cause mutational damage to DNA, so if victims are fortunate enough to survive the initial insult, they may still have significant long term health repercussions. Arsenic and mustards are known for this, and carry risks of skin and haematological malignancy in the longer term. Arsenic can also accelerate atherosclerosis.
- **ricin poisoning**: Laboratory findings in ricin inhalation are non-specific but similar to other pulmonary irritants which cause pulmonary oedema. When inhaled as a small particle aerosol, this toxin may produce pathologic changes within 8 hours and severe respiratory symptoms followed by acute hypoxic respiratory failure in 36-72 hours. An affected patient may have massive bleeding from the stomach and intestines. The patient is most likely to die from multiple organ failure.
- Ricin's toxicity lies in its ability to inhibit protein synthesis, via the endonuclease activity of its A-chain.

Organophosphate insecticide poisoning

One of the effects of organophosphate poisoning is **irreversible inhibition of acetylcholinesterase** (for example, **malathion** and **parathion**)

Features can be predicted by the accumulation of acetylcholine at muscarinic and nicotinic synapses.

(Mnemonic = MSLUD + hypotension, bradycardia)

- miosis, muscle fasciculation Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia, heart block
- Wheeze , pulmonary edema
- tremors , confusion & coma

Muscarinic effects include:

- Nausea, Vomiting
- Abdominal pains, and
- Urinary and faecal incontinence.
- Vision may be blurred.

In severe poisoning the following may occur:

- Bradycardia
- Hypotension
- Heart block, and
- Pulmonary oedema.
- Increased pulmonary parasympathetic tone can result in wheezing due to bronchial hypersecretion and bronchospasm.
- Increased parasympathetic tone to salivary glands leads to hypersalivation.

Nicotinic side effects include:

- Twitching, Fasciculations
- Muscle weakness
- Tachycardia, and
- Hypertension.

Central nervous system effects include:

- Anxiety
- Tremor
- Confusion, and
- Coma.

Management:

- **Atropine**
- the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

malathion 0.5% used in treatment of scabies

- Sarin gas and related agents cause inhibition of the enzyme acetylcholinesterase, causing levels of acetylcholine to build up in the nervous system causing prolonged sustained contraction of the diaphragm. This hinders and eventually paralyses normal breathing.

Botulinum toxin

As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications:

- 1) blepharospasm
- 2) hemifacial spasm
- 3) spasmodic torticollis
- 4) focal spasticity including:
 - ✓ CP patients,
 - ✓ hand and wrist disability associated with stroke
- 5) severe hyperhidrosis of the axillae
- 6) achalasia

Scombroid poisoning

- Scombroid poisoning is associated with consumption of *Scombridae*, dark meat fish such as **tuna**, **mackerel** and **marlin**.
- The symptoms are due to ingestions of amines, predominantly **histamines**, produced by bacterial decarboxylation of histidine in fish meat.
- The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature.
- Cooking does not inactivate the toxin/histamines.
- The illness is usually self-limiting and the severity is dependent on the amount of fish ingested, symptoms are worse when a large amount of fish is ingested.
- Onset is usually **10-30 minutes** post-ingestion of the implicated fish but a delayed onset may occur up to 2 hours.

The symptoms that occur are typically associated with histamine such as

- 1) Headache
 - 2) Dizziness
 - 3) Palpitations
 - 4) Nausea, Abdominal pain, Diarrhoea
 - 5) Urticarial rash
 - 6) Bronchospasm and
 - 7) Hypotension or hypertension.
- Patients with pre-existing conditions such as bronchial asthma, and those taking isoniazid (a histaminase inhibitor) may be more symptomatic.

Management:

- ☒ Specific treatment is usually unnecessary and most symptoms subside between two and 36 hours.
- 1) **In severe cases:** symptoms respond rapidly to **antihistamines**, for example, chlorpheniramine and IV cimetidine by slow IV injection over at least 5 minutes.
 - 2) **Adrenaline** is required in rare, **very severe cases**.
 - 3) There is **no role for** routine **corticosteroid** use.

Saxitoxin

- A **neurotoxin** produced by dinoflagellates and proliferates when sea temperatures rise in spring and summer and often make the sea look red in colour ('**red tide**').
- Various molluscs such as mussels, clams, and cockles may concentrate saxitoxin during such 'red tide'.

Clinical symptoms such as

- Dizziness
 - Incoordination
 - Weakness
 - Numbness and Paraesthesia
- ☒ Can occur within minutes and up to 10 hours post-ingestion of saxitoxin
 - ☒ **Respiratory failure** (due to muscle weakness) may develop.

Snake Bite

- The **adder** (*Vipera berus*) is the only poisonous indigenous snake in the United Kingdom.
- Most adder bites occur in the summer months to people walking in long grass or heathland and typically occur on the ankle and lower leg.
- Only 50% of bites are associated with true envenomation as snakes do not always inject venom when they bite.

Local symptoms and signs include

- 1) Pain, swelling and Bruising at the site of the bite and
- 2) Painful regional lymphadenopathy.

Systemic features of envenomation:

- 1) **Early anaphylactoid symptoms** that include:
 - ☒ nausea, vomiting, abdominal pain, diarrhoea,
 - ☒ transient hypotension with syncope,
 - ☒ angioedema or urticaria
 - 2) **Some patients later have:**
 - ☒ persistent hypotension, ECG abnormalities,
 - ☒ coagulopathy or spontaneous bleeding,
 - ☒ adult respiratory distress syndrome, and
 - ☒ acute renal failure
- There is frequently a leukocytosis ($WBC > 15 \times 10^9/L$) and
 - Serum creatine kinase may be **elevated**.
 - Fatalities are rare following adder bites, though they may be associated with significant morbidity especially tissue necrosis at the site of the bite in adults.

Treatment:

- ☒ usually supportive
- ☒ The bitten limb should be immobilised and a ligature is not necessary unless a delay is anticipated before admission to hospital.
- ☒ Any patient who shows signs of envenomation needs to be admitted to hospital and monitored for 24 hours.
- ☒ Regular monitoring should consist of:
 - measurement of pulse, blood pressure, urine output and
 - the degree of swelling of the bitten limb should be recorded
- ☒ Early anaphylactoid symptoms may be treated with **adrenaline**.
- ☒ **European viper venom antiserum** should be considered in the following situations:
 - 1) Persistent hypotension
 - 2) ECG abnormalities
 - 3) Haemostatic abnormalities
 - 4) Marked local tissue swelling extending proximally (extending above the ankle or wrist [if bitten on the hand/foot] within **4 hours** of the bite).

- Antivenom is given by IV injection over 10-15 minutes or by IV infusion over 30 minutes and may be repeated after 12 hours if symptoms of systemic envenoming persist.
- Anaphylactic reactions occur in 1% of patients during administration of antivenom and a history of asthma or other allergy is a relative contraindication to its use.
- **Adrenaline** should be available for immediate use while the antivenom is infused in case a severe anaphylactic reaction occurs.

The weeverfish (*Trachinus vipera*) سمك الطرخين

- The weeverfish lives in shallow waters around the coast of the United Kingdom.
- This small, sandy-coloured fish has sharp dorsal opercular spines that are attached to subcutaneous poison glands.
- Most stings from the weeverfish occur in the summer months in bare-footed bathers who step on the fish in shallow water, but stings also occur in anglers الصيادين who attempt to grasp the fish when caught on a line.
- The sting of the fish causes intense pain at the site of the wound.
- The toxin produced by the fish is **heat-labile** and is denatured at temperatures **> 40°C**.
- Treatment of a weeverfish sting should include cleansing of the wound and immersion in **hot water** (as hot as can be borne), **ideally around 45°C**.

The Portuguese man-of-war

رجل الحرب البرتغالي أو قناديل البحر

- The jellyfish with the most severe sting in British waters is the Portuguese man-of-war.
- The Portuguese man-of-war (*Physalia physalis*) - actually a form of plankton and not a jellyfish - can give a fatal sting in susceptible individuals.
- It is a distinctive light blue colour and typically floats on the surface of the water and has a characteristic crenellated dorsal 'sail'. شراع علي ظهره
- Other endogenous jellyfish species in coastal waters around the United Kingdom include the lion's mane jellyfish (*Cyanea capillata*) which have been reported in increased numbers around the shores of the UK in recent years, and the moon jellyfish (*Aurelia aurita*) which are common throughout British waters. The latter two jellyfish have a relatively mild sting.

Management:

- ⊗ Patients stung by jellyfish should be removed from the sea as soon as possible.
- ⊗ Adherent tentacles مخابل should be removed from the skin carefully (wearing gloves or using tweezers) or washed off with seawater.
- ⊗ ~~Alcoholic solutions~~ including ~~suntan~~ lotions should not be applied to any jellyfish sting because they may cause further discharge of stinging hairs.
- ⊗ The optimal treatment for jellyfish stings is unclear.
- ⊗ Both **ice packs** and **heat packs** have been shown to reduce pain and which to use may be a matter of patient choice as to which provides the most relief.
- ⊗ Acetic acid solution may provide symptomatic relief for most jellyfish stings from UK species
- ⊗ However, it has been shown that sting cells from the Portuguese man-of-war discharge in response to acetic acid and vinegar solutions should therefore be avoided when this species is known to be the cause of the sting.
- ⊗ Slurry of **sodium bicarbonate** has been shown to be of benefit in treating stings from all UK species and is therefore a better choice when it is uncertain which species is responsible.
- ⊗ Application of urine has no role in the treatment of jellyfish stings in the UK and is of dubious benefit in stings from other species worldwide.



Dopamine receptor agonists

- e.g bromocriptine, cabergoline, ropinirole, apomorphine

Indications:

- 1) Parkinson's disease
 - 2) prolactinoma/galactorrhoea
 - 3) cyclical breast disease
 - 4) acromegaly
- Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist.
 - If the patient is elderly, L-dopa is sometimes used as an initial treatment
 - Ergot-derived dopamine receptor agonists (**bromocriptine, cabergoline, pergolide***) have been associated with pulmonary, retroperitoneal and cardiac fibrosis.
 - The Committee on Safety of Medicines advice that an echo, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

Adverse effects:

- 1) nausea/vomiting
- 2) postural hypotension, nasal congestion
- 3) hallucinations, impulse control disorders
- 4) daytime somnolence,

*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of **valvular dysfunction**

Octreotide

- long-acting analogue of **somatostatin**
- somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin

Uses:

- 1) **Acute treatment of variceal haemorrhage**
- 2) **Prevent complications following pancreatic surgery**
- 3) **acromegaly**
- 4) **carcinoid syndrome**
- 5) **VIPomas**
- 6) **refractory diarrhoea**

Adverse effects:

- gallstones (secondary to biliary stasis)

Phenytoin

Phenytoin is used to in the management of seizures (**1b antiarrhythmic**)

Mechanism of action:

- ☒ **sodium channel blocker**,
- ☒ decreasing the sodium influx into neurons which in turn decreases excitability

Adverse effects:

Acute:

- 1) Initially: dizziness, diplopia, nystagmus, slurred speech, ataxia
- 2) later: confusion, seizures

Chronic:

- 1) common:
 1. gingival hyperplasia (secondary to increased expression of platelet derived growth factor, PDGF),
 2. hirsutism, Acne
 3. coarsening of facial features,
 4. drowsiness
- 2) megaloblastic anaemia (secondary to **altered folate metabolism**)
- 3) enhanced vitamin D metabolism causing **hypocalcaemia & Osteomalacia**
- 4) peripheral neuropathy
- 5) **cerebellar syndrome**
- 6) dyskinesia
- 7) Lymphadenopathy

Idiosyncratic:

- 1) **fever**
- 2) rashes, including severe reactions such as **toxic epidermal necrolysis**
- 3) **hepatitis**
- 4) Dupuytren's contracture
- 5) aplastic anaemia
- 6) drug-induced lupus

Teratogenic:

- associated with **cleft palate** and **congenital heart disease**

Sodium valproate

- Sodium valproate is used in the management of epilepsy
- First line therapy for **generalised seizures**.
- It works by **increasing GABA activity**.

Adverse effects

- 1) nausea
- 2) increased appetite and weight gain
- 3) alopecia: regrowth may be curly
- 4) ataxia
- 5) tremor
- 6) hepatitis, pancreatitis
- 7) thrombocytopaenia
- 8) teratogenic
- 9) hyponatraemia
- 10) Polycystic ovary disease PCO

Drug causes of urticaria

The following drugs commonly cause urticaria:

- 1) aspirin
- 2) NSAIDs
- 3) penicillins
- 4) opiates

Drug-induced impaired glucose tolerance

- 1) thiazides,
- 2) furosemide (less common)
- 3) steroids
- 4) tacrolimus, ciclosporin
- 5) interferon-alpha
- 6) nicotinic acid
- 7) atypical antipsychotics e.g. olanzapine
- 8) Beta-blockers cause a slight impairment of glucose tolerance. They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

Drugs causing ocular problems

Cataracts

- steroids

Corneal opacities

- 1) amiodarone
- 2) indomethacin

Optic neuritis

- 1) ethambutol
- 2) amiodarone
- 3) metronidazole

Retinopathy

- chloroquine, quinine

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drug-induced liver disease

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver

The following drugs tend to cause a hepatocellular picture:

- 1) paracetamol
- 2) sodium valproate, phenytoin
- 3) MAOIs
- 4) halothane
- 5) anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- 6) statins
- 7) alcohol
- 8) amiodarone
- 9) methyldopa

The following drugs tend to cause cholestasis (+/- hepatitis):

- 1) oral contraceptive pill
- 2) anabolic steroids, testosterone
- 3) antibiotics: flucloxacillin, co-amoxiclav, erythromycin* , nitrofurantoin
- 4) Antipsychotics: phenothiazines: chlorpromazine, prochlorperazine
- 5) sulphonylureas
- 6) fibrates
- 7) rare reported causes: nifedipine

*risk may be reduced with erythromycin stearate

Liver cirrhosis:

- 1) methotrexate
- 2) methyldopa
- 3) amiodarone

Drug-induced pancytopenia

- 1) cytotoxics
- 2) trimethoprim, chloramphenicol
- 3) gold, penicillamine (anti-rheumatoid)
- 4) carbimazole (anti thyroid)
- 5) carbamazepine (anti-epileptics)
- 6) sulphonylureas, tolbutamide

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- 1) quinine
- 2) Abciximab
- 3) NSAIDS
- 4) furosemide
- 5) penicillins, sulphonamides, rifampicin, linezolid
- 6) carbamazepine, valproate
- 7) heparin

Gingival hyperplasia

- 1) phenytoin
- 2) ciclosporin
- 3) calcium channel blockers (especially nifedipine)
- 4) AML (myelomonocytic and monocytic types)

Osteoporosis management:

See Rheumatology

Nephrotic syndrome: causes

Primary GN (80% of cases)

- minimal change glomerulonephritis (causes 80% in children, 30% in adults)
- membranous glomerulonephritis
- focal segmental glomerulosclerosis
- membranoproliferative glomerulonephritis

Systemic disease (about 20%)

- diabetes mellitus
- systemic lupus erythematosus
- amyloidosis

Drugs

- gold (sodium aurothiomalate), penicillamine

Others

- congenital
- neoplasia: carcinoma, lymphoma, leukaemia, myeloma
- infection: bacterial endocarditis, hepatitis B, malaria

Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common

Drugs to avoid in renal failure:

- 1) antibiotics: tetracycline, nitrofurantoin
- 2) NSAIDs
- 3) lithium
- 4) metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- 1) most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- 2) digoxin, atenolol
- 3) methotrexate
- 4) sulphonylureas
- 5) furosemide
- 6) opioids

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease:

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

Urinary incontinence

- Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population.
- It is more common in elderly females.

Causes:

- 1) overactive bladder (OAB)/urge incontinence: due to detrusor over activity
- 2) stress incontinence: leaking small amounts when coughing or laughing
- 3) mixed incontinence: both urge and stress
- 4) overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement

Initial investigation:

- 1) **bladder diaries** should be completed for a minimum of 3 days
- 2) vaginal examination to exclude cystocele
- 3) urine dipstick and culture

Management:

Depends on whether urge or stress UI is the predominant picture.

☒ If urge incontinence is predominant:

- 1) bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- 2) bladder stabilising drugs: **antimuscarinic** is **first-line**
- 3) surgical management: e.g. **sacral nerve stimulation**

☒ If stress incontinence is predominant:

- 1) pelvic floor muscle training (for a minimum of 3 months)
- 2) surgical procedures: e.g. retropubic mid-urethral tape procedures

Proton pump inhibitors

- A group of drugs which profoundly reduce acid secretion in the stomach.
- They irreversibly blocking the **hydrogen/potassium ATPase** enzyme system (the H^+/K^+ ATPase) of the gastric parietal cell
- Examples include omeprazole and lansoprazole

Sildenafil

Sildenafil is a **phosphodiesterase type V inhibitor** used in the treatment of impotence.

Contraindications:

- 1) patients taking nitrates and related drugs such as nicorandil
- 2) hypotension
- 3) recent stroke or MI (NICE recommend waiting 6 months)
- 4) non-arteritic anterior ischaemic optic neuropathy

Side-effects:

- 1) visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic optic neuropathy
- 2) nasal congestion
- 3) flushing
- 4) headache
- 5) gastrointestinal side-effects

Smoking cessation

NICE released guidance in 2008. General points:

- 1) patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion NICE state that clinicians should not favour one medication over another
- 2) NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- 3) Prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- 4) if unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- 5) do not offer NRT, varenicline or bupropion in any combination

Nicotine replacement therapy:

- **Adverse effects:** nausea & vomiting, headaches and flu-like symptoms
- NICE recommend offering a combination of nicotine patches and another form of NRT (as gum, lozenge, inhalator or nasal spray) to:
 - ☒ people who show a high level of dependence on nicotine or
 - ☒ who have found single forms of NRT inadequate in the past

Varenicline:

- a **nicotinic receptor partial agonist**
- should be started **1 week** before the patient's target date to stop
- the recommended course of treatment is **12 weeks** (but patients should be monitored regularly and treatment only continued if not smoking)
- has been shown in studies to be **more effective** than bupropion

Adverse effects:

- Nausea is the most common adverse effect.
- Other common problems include headache, **insomnia, abnormal dreams**
- varenicline should be used with caution in patients with a history of depression or self-harm. There are ongoing studies looking at the **risk of suicidal** behaviour in patients taking varenicline
- contraindicated in pregnancy and breast feeding

Bupropion

Mechanism of action:

- ☒ **a norepinephrine and dopamine reuptake inhibitor**, and
- ☒ **nicotinic antagonist**
- should be started 1 to 2 weeks before the patient's target date to stop
- small risk of **seizures** (1 in 1,000)
- Contraindicated in epilepsy, pregnancy and breast feeding.
- Having an **eating disorder** is a relative contraindication

Pregnant women

- NICE recommended in 2010 that all pregnant women should be tested for smoking
- Use carbon monoxide detectors,
- Partly because 'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense'.
- All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

Interventions:

- ☒ the first-line interventions in pregnancy should be **cognitive behaviour therapy**, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- ☒ The evidence for the use of **NRT in pregnancy** is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birthweight. Pregnant women should remove the patches before going to bed
- ☒ as mentioned above, varenicline and bupropion are contraindicated

Palliative care prescribing

Agitation and confusion

- Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication.
 - If specific treatments fail then the following may be tried:
 - 1) **first choice:** haloperidol
 - 2) other options: chlorpromazine, levomepromazine
- ☒ In the terminal phase of the illness then agitation or restlessness is best treated with midazolam (dormicum)

Hiccups

Management of hiccups:

- 1) chlorpromazine (typical anti-psychotic) is licensed for treatment of intractable hiccups
- 2) haloperidol, gabapentin are also used
- 3) dexamethasone is also used, particularly if there are hepatic lesions

Prescribing in pregnant patients

- Very few drugs are known to be completely safe in pregnancy.
- Some countries have developed a grading system.

Drugs known to be harmful:

Antibiotics

- tetracyclines
- aminoglycosides
- sulphonamides and trimethoprim
- quinolones: the BNF advises to avoid due to arthropathy in some animal studies

Other drugs

- ACE inhibitors, angiotensin II receptor antagonists
- statins
- warfarin
- sulfonylureas
- retinoids (including topical)
- cytotoxic agents

The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk

Breast feeding

Contraindications

- The major breastfeeding contraindications tested in exams relate to drugs (see below).
- Other contraindications of note include:
 - 1) **galactosaemia**
 - 2) **Viral infections:**
 - ☒ This is controversial with respect to HIV in the developing world.
 - ☒ This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

Drugs that can be given to mothers who are breast feeding:

- 1) Penicillins, cephalosporins, trimethoprim
- 2) glucocorticoids (avoid high doses), levothyroxine*
- 3) sodium valproate, carbamazepine
- 4) salbutamol, theophyllines
- 5) TCAs, antipsychotics (clozapine should be avoided)
- 6) Beta-blockers, hydralazine, methyldopa
- 7) warfarin, heparin
- 8) digoxin

*BNF advises that the amount is too small to affect neonatal hypothyroidism screening

The following drugs should be avoided:

- 1) ciprofloxacin, tetracycline, chloramphenicol, sulphonamides
- 2) lithium, benzodiazepines, clozapine
- 3) carbimazole, sulphonylureas
- 4) aspirin
- 5) amiodarone
- 6) cytotoxic drugs

Hormone replacement therapy (HRT)

- It involves the use of a small dose of oestrogen (combined with a **progestogen** in women with a uterus) to help **alleviate menopausal symptoms**.
- The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

Indications:

- 1) vasomotor symptoms such as flushing, insomnia and headaches
 - 2) premature menopause: should be continued until the age of 50 years
 - 3) osteoporosis: but should only be used as **second-line treatment**
- The main indication is the control of vasomotor symptoms.
 - The other indications such as reversal of vaginal atrophy and prevention of osteoporosis should be treated with other agents as first-line therapies
 - Other benefits include a reduced incidence of colorectal cancer

Side-effects:

- 1) nausea
- 2) breast tenderness
- 3) fluid retention and weight gain

Potential complications:

- 1) Increased risk of **endometrial cancer**:
 - Reduced by the addition of a progestogen but not eliminated completely.
 - The BNF states that the additional risk is eliminated if a progestogen is given continuously
- 2) increased risk of **breast cancer**: increased by the addition of a progestogen
- 3) increased risk of **venous thromboembolism**: increased by the addition of a progestogen
- 4) Increased risk of **stroke**: The BNF states that the stroke risk is the same regardless of whether the HRT preparation contains progesterone.
- 5) increased risk of **IHD** if taken > 10 years **after menopause**

Breast cancer

- in the Women's Health Initiative (WHI) study there was a relative risk of **1.26 at 5 years** of developing breast cancer
- the increased risk relates to duration of use
- breast cancer incidence is higher in women using combined preparations compared to oestrogen-only preparations
- the risk of breast cancer begins to decline when HRT is stopped and by **5 years** it reaches the same level as in women who have never taken HRT

Progestogen.....Breast cancer..... **PB**

Estrogen.....Endometrial cancer**EE**

Combined oral contraceptive pill

- The decision of whether to start a woman on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (UKMEC).
- This scale categorises the potential cautions and contraindications according to a four point scale:

UKMEC 1: condition for which there is no restriction for the use of the contraceptive method

UKMEC 2: advantages generally outweigh the disadvantages

UKMEC 3: disadvantages generally outweigh the advantages

UKMEC 4: represents an unacceptable health risk

<u>Examples of UKMEC 3 conditions</u>	<u>Examples of UKMEC 4 conditions</u>
1) more than 35 years old and smoking < 15 cigarettes/day 2) BMI > 35 kg/m²* 3) migraine without aura and more than 35 years old 4) family history of thromboembolic disease in first degree relatives < 45 years 5) controlled hypertension 6) immobility e.g. wheel chair use 7) breast feeding 6 weeks - 6 months postpartum	1) more than 35 years old and smoking >15 cigarettes/day 2) migraine with aura 3) history of thromboembolic disease or thrombogenic mutation 4) history of stroke or ischaemic heart disease 5) uncontrolled hypertension 6) major surgery with prolonged immobilisation 7) breast feeding < 6 weeks post-partum 8) breast cancer

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

*The UKMEC 4 rating for a BMI > 40 kg/m² was removed in 2009.

Progestogen only pill

Advantages:

- 1) highly effective (failure rate = 1 per 100 woman years)
- 2) contraceptive effects reversible upon stopping
- 3) doesn't interfere with sex
- 4) can be used whilst breast-feeding
- 5) can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

Disadvantages:

- 1) Irregular periods: some users may not have periods whilst others may have irregular or light periods. This is the most common adverse effect
- 2) doesn't protect against STIs
- 3) increased incidence of functional ovarian cysts
- 4) Common side-effects include breast tenderness, weight gain, acne and headaches. These symptoms generally subside after the first few months

Tamoxifen

- A selective estrogen receptor modulator (SERM)
- Acts as an oestrogen receptor **antagonist** and **partial agonist**.
- It is used in the management of oestrogen receptor positive **breast cancer**

Adverse effects:

- 1) menstrual disturbance: vaginal bleeding, amenorrhoea
- 2) hot flushes
- 3) venous thromboembolism
- 4) endometrial cancer

Tamoxifen is typically used for 5 years following removal of Breast tumour.

Raloxifene (SERM):

- A pure oestrogen receptor antagonist, and
- carries a lower risk of endometrial cancer

Antibiotics

Bactericidal vs. bacteriostatic

Bactericidal antibiotics:

- 1) penicillins
- 2) cephalosporins
- 3) aminoglycosides
- 4) nitrofurantoin
- 5) metronidazole
- 6) quinolones
- 7) rifampicin
- 8) isoniazid

Bacteriostatic antibiotics

- 1) chloramphenicol
- 2) macrolides
- 3) sulphonamides
- 4) tetracyclines
- 5) trimethoprim

Mechanisms of action

The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation:

- 1) penicillins
- 2) cephalosporins

Inhibit protein synthesis:

- 1) aminoglycosides (cause misreading of mRNA)
- 2) chloramphenicol
- 3) macrolides (e.g. erythromycin)
- 4) tetracyclines
- 5) fusidic acid
- 6) Quinopristin & dalfopristin

Inhibit DNA synthesis:

- 1) quinolones (e.g. ciprofloxacin)
- 2) metronidazole
- 3) sulphonamides
- 4) trimethoprim

Inhibit RNA synthesis

- rifampicin

Anaerobic activity

The following antibiotics have anti-anaerobic activity

- 1) penicillins
- 2) cephalosporins (except ceftazidime)
- 3) erythromycin
- 4) metronidazole
- 5) tetracycline

The following antibiotics do not have anti-anaerobic activity GCC

- 1) gentamicin
- 2) ciprofloxacin
- 3) ceftazidime

Linezolid

- Linezolid is a type of oxazolidinone antibiotic which has been introduced in recent years.
- It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex
- It is bacteriostatic nature.

Spectrum: highly active against Gram positive organisms including:

- 1) MRSA (Methicillin-resistant Staphylococcus aureus)
- 2) VRE (Vancomycin-resistant enterococcus)
- 3) GISA (Glycopeptide Intermediate Staphylococcus aureus)

Adverse effects:

- 1) thrombocytopenia (reversible on stopping)
- 2) MAOI monoamine oxidase inhibitor: avoid tyramine containing foods (Cheese reaction)

Macrolides

- Erythromycin was the first macrolide used clinically.
- Newer examples include clarithromycin and azithromycin.
- Macrolides act by inhibiting bacterial protein synthesis.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Adverse effects:

- 1) GIT side effects are common. Nausea is less common with clarithromycin than erythromycin
- 2) cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- 3) P450 inhibitor

Common interactions:

- ☒ **Statins** should be stopped whilst taking a course of macrolides:
 - ⇒ Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins.
 - ⇒ Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.

Quinupristin & dalfopristin

- injectable streptogramin antibiotic
- combination of group A and group B streptogramin
- inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum:

- most Gram positive bacteria except *Enterococcus faecalis**

Adverse effects

- 1) thrombophlebitis (give via a central line)
- 2) arthralgia
- 3) P450 inhibitor

*not to be confused with *Enterococcus faecium*, which is sensitive to Quinupristin & dalfopristin

Quinolones

- Quinolones are a group of antibiotics which work by **inhibiting DNA synthesis**.
- They are bactericidal in nature. Examples include:
 - 1) ciprofloxacin
 - 2) levofloxacin

Mechanism of action:

- inhibit topoisomeras II (DNA gyrase) and topoisomerase IV

Adverse effects:

- 1) lower seizure threshold in patients with epilepsy
- 2) tendon damage (including rupture) - the risk is increased in patients also taking steroids
- 3) cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children

Teicoplanin (Targocid)

- Used in prophylaxis and treatment of serious infections by Gram+ve bacteria, including MRSA & Enterococcus faecalis
- It is a semisynthetic glycopeptide with a spectrum similar to vancomycin.
- It inhibits bacterial cell wall synthesis.

Tigecycline (Tygacil)

- Was developed in response to growing prevalence of Ab. resistance in bacteria as Staph. aureus and Acinetobacter baumannii.
- Tygacil is the first clinically available drug in a new class called glycylcyclines.
- It is structurally similar to tetracyclines (contains a central 4-ring carbocyclic skeleton and is a derivative of minocycline).
- Tigecycline is bacteriostatic (protein synthesis inhibitor by binding to the 30S ribosomal subunit)

Cross-reactivity between classes of β -lactam antibiotics

- β -lactam antibiotics: **penicillins, cephalosporins and carbapenems**
- An IgE mediated reaction to a β -lactam based antibiotic.
- These reactions typically occur within minutes to hours of exposure, however, if this is the first exposure it can present later in the course of the treatment.
- Such reactions may demonstrate cross-reactivity between classes of β -lactam antibiotics (**penicillins, cephalosporins and carbapenems**).
- Rates of cross-reactivity between penicillins and cephalosporins are often quoted at around 10% though likely to be somewhat lower.
- Cross-reactivity is less frequent with carbapenem class antibiotics such as meropenem but still a risk.

The Jarisch-Herxheimer reaction

- This is an acute febrile illness with headache, myalgia, chills and rigors starting within 12 hours of the first dose of treatment and resolving within 24 hours.
- It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.
- It occurs in ~50% of patients with primary syphilis, 90% with secondary syphilis and 25% with early latent syphilis.
- It is very rare in late syphilis but may be dangerous if there are lesions around important anatomical sites (for example, sinoatrial node, larynx).
- The reaction is thought to occur due to the release of endotoxin from killed microorganisms and is accompanied by a rise in pro-inflammatory cytokines.
- The reaction was originally described with syphilis treatment but is also well described in rickettsial diseases such as Lyme disease and Q fever.
- Patients should be counselled about the reaction prior to receiving therapy for syphilis.
- There is no meningism and the evolving rash is blanching.
- A single dose of benzathine penicillin should cure most cases of early syphilis, thus no further antibiotics should be necessary.
- This reaction can easily be confused with an allergic reaction, but will settle without treatment.
- Simple reassurance and consideration of the use of paracetamol for symptom control is the appropriate management.

Anti-retrovirals (HIV)

- Highly active anti-retroviral therapy (HAART) involves a combination of at least 3 drugs,
 - 1) Typically two nucleoside reverse transcriptase inhibitors (**NRTI**)
And either
 - 2) a protease inhibitor (**PI**) or
 - 3) a non-nucleoside reverse transcriptase inhibitor (**NNRTI**)
- This combination both decreases viral replication but also reduces the risk of viral resistance emerging

A) Nucleoside reverse transcriptase inhibitor (NRTI):

Examples: zidovudine (AZT), lamivudine, didanosine, stavudine, zalcitabine

Side-effects:

- 1) general NRTI side-effects: peripheral neuropathy, lactic acidosis
- 2) **Zidovudine:** anaemia, neutropenia, pancytopenia, (BM suppression), myopathy, **rhabdomyolysis**, **lactic acidosis** & black nails
- 3) **Didanosine:** **pancreatitis**

B) Non-nucleoside reverse transcriptase inhibitors (NNRTI):

Examples: nevirapine, efavirenz

Side-effects:

- 1) P450 enzyme interaction (nevirapine induces),
- 2) hepatitis
- 3) Rashes (nevirapine causes rash in 15%)

Nevirapine (NVP)

- Causes **hypersensitivity reactions** and **hepatotoxicity**.

Efavirenz

- The most common HAART drug associated with **gynecomastia**.
- Gynaecomastia is one of the less common side effects of efavirenz together with the more common **neuropsychiatry** side effects.
- efavirenz is a **strong enzyme inducer**

C) Protease inhibitors (PI)

Examples: indinavir, nelfinavir, ritonavir, saquinavir

Side-effects:

- 1) diabetes,
- 2) hyperlipidaemia,
- 3) buffalo hump,
- 4) central obesity,
- 5) P450 enzyme inhibition

☒ **Indinavir:**

- 1) renal stones,
- 2) asymptomatic hyperbilirubinaemia

☒ **ritonavir:** a potent inhibitor of the P450 system

- + HAART are frequent causes of anaemia in HIV-seropositive patients. Of these, zidovudine (AZT) most frequently causes **anaemia**, usually by **bone marrow suppression** and patients can become transfusion-dependent in severe cases.
- + **Macrocytosis** is a typical finding in patients on AZT and can be used as a parameter to monitor adherence to therapy.
- + Simvastatin is contraindicated in patients on protease inhibitors and plasma levels of atorvastatin are also greatly elevated in these patients. For this reason, **pravastatin** is usually the drug of choice.

Abacavir (ABC)

Causes mainly hypersensitivity reactions and gastrointestinal disturbances

Lopinavir/ritonavir

Cause metabolism abnormalities and gastrointestinal disturbances

Cytotoxic agents

Alkylating agents

Cyclophosphamide

- An alkylating agent used in the management of cancer and autoimmune conditions.
- It works by causing **cross-linking of DNA**

Adverse effects:

1) **haemorrhagic cystitis:**

- ✓ incidence reduced by the use of hydration and mesna
- ✓ Cyclophosphamide may be converted to urotoxic metabolites such as acrolein.
- ✓ Mesna binds to these metabolites through its sulfhydryl-moieties and reduces the incidence of haemorrhagic cystitis

2) **transitional cell carcinoma**

3) **myelosuppression**

4) **premature ovarian failure** and **infertility in men and women**, **risk** increases with increasing dose

Cyclophosphamide - haemorrhagic cystitis - prevent with mesna

Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	• Stabilizes DNA-topoisomerase II complex • inhibits DNA & RNA synthesis	Cardiomyopathy

Antimetabolites

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	1) Myelosuppression, 2) mucositis, 3) liver fibrosis, 4) lung fibrosis
Fluorouracil (5-FU)	- Pyrimidine analogue - inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	1) Myelosuppression, 2) mucositis, 3) dermatitis
6mercaptopurine	- Purine analogue - activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	- Pyrimidine antagonist. - Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	1) Myelosuppression, 2) Ataxia

Acts on microtubules

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	Vincristine: 1) Peripheral neuropathy (reversible) , 2) paralytic ileus Vinblastine: myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin	Neutropaenia Typhlitis or neutropenic colitis is a rare but serious complication of profound neutropenia which requires IV antibiotics .

Other cytotoxic drugs

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	1) Ototoxicity, 2) peripheral neuropathy, 3) hypomagnesaemia
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

Chemotherapy side-effects:

Nausea and vomiting

- Nausea and vomiting are common side-effects of chemotherapy.
- Risk factors for the development of symptoms include:
 - ✓ anxiety
 - ✓ age less than 50 years old
 - ✓ concurrent use of opioids
 - ✓ the type of chemotherapy used
- For patients at low-risk of symptoms then drugs such as **metoclopramide** may be used first-line.
- For high-risk patients then 5HT3 receptor antagonists such as **ondansetron** are often effective, especially if combined with dexamethasone

Haemorrhagic Cystitis:

- Presentation occurs along a spectrum of disease ranging from irritative voiding symptoms with mild haematuria to massive haematuria with the passage of clots (which may induce clot retention).
 - Cyclophosphamide therapy is the most common cause of haemorrhagic cystitis.
 - The risk is dose related and related to production of acrolein, a urothelial toxic metabolite.
 - Although the whole urothelium is at risk the bladder is most commonly affected due to the longer contact time with the toxin.
 - The risk of haemorrhagic cystitis is increased in dehydrated patients.
 - Mesna is a drug that reacts with acrolein both inactivating it and acting to prevent its formation. When administered alongside intravenous cyclophosphamide it reduces the risk of haemorrhagic cystitis.
 - Alum and formalin may be used as bladder irrigating agents in cases of haemorrhagic cystitis in order attempt to arrest haemorrhage from the urothelium in severe cases.
 - Steroids are not used in the management of haemorrhagic cystitis and antibiotics are only indicated where there is evidence of bacterial infection.
- =====

A 68-year-old woman is taking long term warfarin for atrial fibrillation and mitral valve prolapse. She requires a right hemi-colectomy for a colon cancer identified on colonoscopy. Her recent INR is 2.2. Which of the following is the correct advice for her anticoagulation?

☐	Discontinue warfarin on the day of surgery
☐	Discontinue warfarin two days before surgery
☒	Discontinue warfarin two days before surgery and commence low molecular weight heparin the following day
☐	Discontinue warfarin five days before surgery and commence low molecular weight heparin 48 hours later
☐	Discontinue warfarin the week before surgery

In addition to discontinuing warfarin five days before surgery and commencing low molecular weight heparin 48 hours later, INR should be checked the day before the procedure to ensure that it is below 1.5.

It is also usual to give the last dose of LMW heparin no less than 12 hours before surgery. Heparin should then be continued after surgery until INR is in the therapeutic range.

Discontinuing warfarin less than five days before surgery runs the risk of significant bleeding complications. Discontinuing warfarin without low molecular weight heparin cover raises the risk of embolic stroke during the peri-surgical period.

Answer D

- **Rivaroxaban** is a highly selective direct factor Xa inhibitor.
- Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the coagulation cascade, inhibiting both thrombin formation and development of thrombi.
- Rivaroxaban does not inhibit thrombin and that it has no effect on platelets
- Rivaroxaban has no activity with respect to factor VII or factor XII.
- Indications for factor Xa inhibition have now been extended to chronic atrial fibrillation.
- Glycoprotein 2b3a inhibition reduces platelet aggregation, inhibitors largely have a role in patients undergoing acute angioplasty.
- Coumarins such as warfarin are vitamin K inhibitors, leading to reduced activity of factors II, VII, IX, X protein C, protein S and protein Z.
- Interaction between co-trimoxazole and warfarin results in enhanced anticoagulant effect. The dose of warfarin should be reduced.

Drugs that induce gynaecomastia include

Inhibitors of testosterone synthesis:

- ketoconazole
- metronidazole
- cimetidine
- etomidate, and
- cisplatin.

Oestrogens:

- digitalis, and
- Oral contraceptive pill.

Other drugs in which the mechanism is not known:

- isoniazid
- diazepam
- omeprazole
- calcium-channel blockers
- ACE inhibitors
- amiodarone
- tricyclic antidepressants
- busulphan
- marijuana
- heroin, and
- spironolactone.

NICE guidelines on the management of [Chronic heart failure \(CG108\)](#) recommend that all patients with left ventricular systolic dysfunction should receive treatment with a beta-blocker and ACE inhibitor licensed for treatment of the condition.

A decline in the glomerular filtration rate (GFR) and a concomitant rise in the creatinine is to be expected when starting treatment with an ACE inhibitor due to their mechanism of action.

Recommendations are taken from the NICE guidelines on the management of [Chronic kidney disease \(CG182\)](#) which state that when initiating ACE inhibitor therapy a 25% reduction in the eGFR or 30% increase in the serum creatinine is tolerable and should not lead to changes in dosing.

ACE inhibitors should also be stopped or dose adjusted if there is a rise in the serum potassium level to greater than 6 mmol/L.

Other causes of a deterioration in renal function should be excluded first before stopping the ACE inhibitor. In this case the patient is taking trimethoprim.

trimethoprim competes with creatinine for excretion in the nephron and as a result will push the serum creatinine value up. The effect can be profound particularly in patients with underlying chronic kidney disease.

Although there has been a significant rise in the eGFR this is calculated based upon the creatinine so cannot be relied upon. If measured the actual glomerular filtration rate should be effectively unchanged.

This patient just meets the criteria for stopping her ACE inhibitor however trimethoprim therapy provides an alternative explanation for the deterioration in renal function. As a result the appropriate option would be to re-check the blood tests in one to two weeks once trimethoprim has been discontinued to see whether the level of renal dysfunction is sustained or improves.

It is likely that a further dose increase would produce greater renal dysfunction, the numbers already demonstrate an unacceptable deterioration from baseline in the both the creatinine and GFR (although there may be an alternative explanation) so a dose increase is not advisable.

Angiotensin receptor blockers produce the same effects as ACE inhibitors in terms of reduction in GFR and rise in creatinine and there is no benefit in changing from one to the other should the other class of drug impair renal function sufficiently that it has to be stopped.

Renal artery stenting may be used in the context of atherosclerotic (or fibromuscular) renal artery stenosis in order to try and control deteriorating renal function or improve control of hypertension. Its use is controversial in some cases.

A profound decline in renal function upon commencing an ACE inhibitor may be indicative, but not diagnostic, of renal artery stenosis.

This patient has a history of left ventricular failure and should be treated with both an ACE inhibitor and a beta-blocker.

NICE guidelines ([CG108 Chronic heart failure](#)) maintain that cardioselective beta-blockers should be tried in patients with left ventricular systolic dysfunction even if they have a diagnosis of:

- Chronic obstructive pulmonary disease (COPD)
- Peripheral vascular disease
- Diabetes
- Erectile dysfunction, or
- Interstitial pulmonary disease.

Beta-blockers should not be commenced in the setting of acute exacerbations of COPD or cardiac failure, but there is no evidence of either in this case.

NICE guidelines on the management of atrial fibrillation ([CG180 Atrial fibrillation](#)) recommend that beta-blockers and rate-limiting calcium channel antagonists should be used first line for rate control.

As the duration of atrial fibrillation is unknown caution should be used when considering the use of drugs which may cardiovert the patient - amiodarone and flecainide.

Additionally long term amiodarone therapy has significant long term complications and is ideally avoided where possible.

Flecainide should be used with caution in patients with structural heart disease or conduction abnormalities and is not recommended in the long term rate control or permanent atrial fibrillation.